DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

March 26, 2010

Todd W. Rich, M.D.
V.P., Regulatory Affairs, Medical Communications
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

RE: BLA 103792
HERCEPTIN® (trastuzumab) Intravenous Infusion
MACMIS #18408

Dear Dr. Rich:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a consumer-directed video (video) entitled "Herceptin Video Storybook - XML Safety Player" (9538100) for HERCEPTIN® (trastuzumab) Intravenous Infusion (Herceptin), submitted by Genentech, Inc. (Genentech) under cover of Form FDA-2253, and also available on the webpage www.herceptin.com[1]. The video is false or misleading because it minimizes the serious risks associated with the use of Herceptin and presents misleading claims regarding the benefits of Herceptin. Thus, the video misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n). *See* 21 CFR 202.1(e)(3)(i); (e)(5)(i) & (ii); (e)(6)(i); (e)(7)(viii).

Background

According to the DESCRIPTION section of its FDA-approved product labeling (PI),[2] "Herceptin (trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2."

According to the INDICATIONS AND USAGE section of its PI, Herceptin is approved for the following indications (emphasis in original):

[1] Available at: http://www.herceptin.com/community/HERStory/storybook.jsp; last accessed March 26, 2010.
[2] The most current version of the FDA-approved PI as of the dissemination date indicated on Form FDA-2253 was the May 22, 2008, version, and that is the version referred to in this letter. We note that the PI for Herceptin has since been updated.

- **Adjuvant Breast Cancer**
  Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [*see Clinical Studies (14.1)*]) breast cancer
  - as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
  - with docetaxel and carboplatin
  - as a single agent following multi-modality anthracycline based therapy.

- **Metastatic Breast Cancer**
  Herceptin is indicated:
  - In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
  - As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

The use of Herceptin is associated with a number of serious and potentially life-threatening risks, including a Boxed Warning for cardiomyopathy, infusion reactions, and pulmonary toxicity. In addition to these warnings, the WARNINGS AND PRECAUTIONS section of the PI also includes warnings regarding the exacerbation of chemotherapy-induced neutropenia, embryo-fetal toxicity, and the need for patients to undergo cardiac monitoring before, during, and after treatment with Herceptin.

In addition to the warnings noted above, the PI details the common adverse reactions that were observed during the clinical trials for Herceptin. According to the PI, common adverse reactions in adjuvant patients (≥2% higher incidence with Herceptin-containing treatment compared with control treatment) included fatigue, infection, neutropenia, anemia, myalgia, dyspnea, rash/desquamation, headache, diarrhea, and nausea. Common adverse reactions in metastatic patients (≥15% incidence with Herceptin monotherapy or ≥5% with Herceptin/paclitaxel therapy) included nausea, fever, infection, rash, increased cough, vomiting, diarrhea, headache, and anemia.

The CLINICAL STUDIES section of the PI includes the following information regarding the increase in median overall survival observed in the clinical trials for Herceptin:

14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer, were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 3752 women, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

Table 6:
Efficacy Results from Adjuvant Treatment of Breast Cancer
(Studies 1 + 2, Study 3, and Study 4)

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
Studies 1 + 2[e]				
AC→TH (n =1872)	133	0.48[a] (0.39, 0.59) p=< 0.0001[b]	62	0.67 p=NS[d]
AC→T (n = 1880)	261		92	
Study 3				
Chemo→ Herceptin (n =1693)	127	0.54 (0.44, 0.67) p=< 0.0001[c]	31	0.75 p=NS[d]
Chemo→ Observation (n = 1693)	219		40	
Study 4[f]				
TCH (n=1075)	134	0.67 (0.54 – 0.84) p=0.0006[b,g]	56	
AC→TH (n=1074)	121	0.60 (0.48 – 0.76) p=< 0.0001[b,g]	49	
AC→T (n=1073)	180		80	

CI = confidence interval.
[a] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.
[b] Stratified log-rank test.
[c] Log-rank test.
[d] NS= non-significant.
[e] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).
[f] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).
[g] A two-sided alpha level of 0.025 for each comparison.

14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n=469 patients). . . . [The trial] studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein.

Table 8:
Study 5: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Median TTP (mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	<0.0001		<0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value[e]	<0.001		<0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quartile	6, 15	4, 8	5,11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] Log-rank test.
[e] $\chi 2$-test.

Minimization of Risk Information

Promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. The main body of the promotional video consists of a 5 ½ minute engaging and lively multi-media presentation that includes:

- Spoken audio that transitions from a dramatic announcer voiceover to testimonials from Herceptin patients, breast cancer advocates, television news reporters, and an oncology nurse;

- constantly changing "storybook" style background visuals; and

- upbeat background music and sound effects (e.g., fireworks).

In contrast, the presentation of the serious risks associated with Herceptin is relegated to a running telescript, which does not include audio, that quickly rolls for 30 seconds prior to the start of the promotional video. The only risk information included in the main body of the video is presented during two patient testimonials as follows:

- "I had mild fatigue, but I managed to keep working, and not miss any of my son's sporting events." (Testimonial given by "Yuriria Campos, Adjuvant Patient;" minute 4:20 of video.)

- "After I completed chemo, I continued with a weekly infusion of Herceptin. I had some serious issues with fatigue, and with muscle and joint pain." (Testimonial given by "Jeri Lynn Cohen, Adjuvant Patient;" minute 4:26 of video.)

The main body of the video omits any discussion of the serious risks associated with Herceptin, including the Boxed Warnings regarding cardiomyopathy, pulmonary toxicity, and infusion reactions. However, this portion of the video includes numerous promotional claims regarding the benefits of Herceptin use. For example, the video states:

- "Finally, big news! The trial's completed, the results promising. The FDA approves the therapy. The first of its kind. It is an exciting moment in the history of cancer treatment. A new hope." (Announcer voiceover, minute 2:28 of video.)

- "And a new drug may act as a roadblock for breast cancer cells in some women." (Female news announcer #1, minute 2:42 of video.)

- "Another new drug in the fight against cancer. One already tested on humans. Stay with us." (Male news reporter #1, minute 2:47 of video.)

- "The drug, Herceptin, is being hailed by doctors. . ." (Female news reporter #2, minute 2:54 of video.)

- "And tonight there's an encouraging new treatment for the cancer that may not be the biggest killer, but it is the one that women fear the most." (Male news reporter #2, minute 2:57 of video.)

- "For oncologists and nurses themselves, the advent of Herceptin meant new hope as well. Finally, the chance to improve survival among their HER2 positive metastatic breast cancer patients." (Announcer voiceover, minute 3:54 of video.)

- "No one knows the value of Herceptin better than the HER2 positive breast cancer patients, who are now moving forward with a positive outlook for the future." (Announcer voiceover, minute 4:08 of video.)

- "To know that there's something there for you, a special targeted therapy." (Testimonial given by "Gay Meehan, Adjuvant Patient;" minute 4:15 of video.)

- "In ten years since its first approval, Herceptin has grown from a visionary approach to cancer treatment, into the standard of care for HER2 positive breast cancer." (Announcer voiceover, minute 4:36 of video.)

- "Trastuzumab was a major step in the direction of getting us to the point where we can target therapy to an individual group's breast cancer." (Testimonial given by "Fran Visco, Breast Cancer Advocate;" minute 4:53 of video.)

By only disclosing the serious risks of Herceptin in the running telescript, the video misleadingly minimizes the risks associated with Herceptin because it fails to convey this important risk information with a prominence and readability reasonably comparable to the claims of effectiveness. The overall effect of this presentation undermines the communication of this important risk information, misleadingly suggesting that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Overstatement of Efficacy/Misleading Claims

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the video includes the following statement (emphasis added):

- "For oncologists and nurses themselves, the advent of Herceptin meant new hope as well. Finally, the chance to <u>improve survival</u> among their HER2 positive metastatic breast cancer patients." (Announcer voiceover; minute 3:54 of video.)
    - Consecutive and/or immediately succeeding background visuals: A woman in a business suit walking in front of a building; a woman exercising on an elliptical machine; the <u>adjuvant</u> patient formerly identified as Ms. Munro turning the pages of a book; the <u>adjuvant</u> patient formerly identified as Ms. Carver-Clarke walking on a treadmill; an instant photo style picture of the <u>adjuvant</u> patient formerly identified as Ms. Munro; a medical caduceus pin in upper right corner of the storybook page.

This presentation is immediately followed by the statement (emphasis added):

- "No one knows the value of Herceptin better than the HER2 positive breast cancer patients, who are now moving forward with a positive outlook for the future." (Announcer voiceover; minute 4:08 of video.)
    - Consecutive and/or immediately succeeding background visuals: Four patients in instant photo style frames with a pink ribbon storybook background - three of the four patients are identified as adjuvant patients, and the three patient testimonials that immediately follow are given by the three adjuvant patients.

The adjuvant patient testimonials above are immediately followed by consecutive visuals of four different professional journal advertisements (journal ads) for Herceptin (emphasis added):

- Journal ad #2 includes the prominent headlines "SURVIVAL," and "HERCEPTIN," as well as a visible Herceptin logo; journal ad #3 includes the prominent headline "Extended Survival with First-Line Power" and the brand name "Herceptin" in the bottom right corner. The applicability of the survival claims in the journal ads to only the metastatic patient population is not visible in the video presentation. (Visuals; minute 4:36 of video.)

Individually and collectively, these presentations overstate the efficacy of Herceptin by implying a proven survival benefit for the adjuvant patient population. However, according to the PI for Herceptin, the observed increase in survival in the adjuvant patient population was not statistically significant. While we note that the survival claim in the announcer voiceover specifies "metastatic breast cancer patients," this is not sufficient to mitigate the misleading impression created by the totality of the presentations in the video that the survival claims made in the audio and visual portions of the video also apply to the featured adjuvant patients.

Additionally, the video states (emphasis added):

- "Thank you for my chance to enjoy my son's life as he grows up, and to be with my husband, and my dogs." (Testimonial given by "Carole Abravaya-Alietti, Metastatic Patient;" minute 5:05 of video.)

According to the PI, the increase in median survival observed in the clinical trials for Herceptin plus chemotherapy as first-line therapy in the metastatic patient population was 4.8 months. Therefore, the suggestion that treatment with Herceptin will allow a woman to watch her son "as he grows up" misleadingly overstates the increase in survival for metastatic breast cancer patients treated with Herceptin plus chemotherapy as first-line therapy, as opposed to those patients treated with chemotherapy alone.

In summary, these claims misleadingly overstate the proven efficacy of Herceptin. If you do, in fact, have data to support these claims, you should submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the video is misleading in violation of the Act, 21 U.S.C. 352(a) & (n). *See* 21 CFR 202.1(e)(3)(i); (e)(5)(i) & (ii); (e)(6)(i); (e)(7)(viii).

DDMAC requests that Genentech immediately cease the dissemination of violative promotional materials for Herceptin such as those described above. Please submit a written response to this letter on or before April 9, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Herceptin that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266; facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18408 in addition to the BLA number for Herceptin. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Herceptin comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

/S/

Cynthia Collins, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications